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September 8, 2003

Dockets Management Branch
U.S. Food and Drug Administration
Department of Health and Human Services
HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 03P-0029
Citizen Petition Submitted by U.S. Stakeholders Group on MDI Transition Requesting that the FDA Initiate a Rulemaking to Remove Albuterol CFC MDIs from the List of Essential Uses of Ozone Depleting Substances – Economic Analysis of Impact on Patients and Payers

Dear Sir or Madam:

On January 29, 2003, the U.S. Stakeholders Group on MDI Transition filed a *Citizen Petition* requesting that the FDA issue a proposed rule to remove albuterol chlorofluorocarbon ("CFC") metered-dose inhalers ("MDIs") from the FDA's list of essential uses of ozone depleting substances. As part of the FDA's analysis prior to removing an essential use, the FDA is considering the impact of costs on patients' access to treatment.

In that regard, we submit the enclosed analysis entitled "The Impact on Patients and Payers of Designating Albuterol a Non-Essential Use of an Ozone Depleting Substance." We prepared this report to assist the FDA in determining whether albuterol CFC MDIs should be removed from the FDA's list of essential uses of ozone depleting substances.

National Economic Research Associates, Inc. ("NERA"), an international firm of economists, was retained by GlaxoSmithKline to analyze the economic issues raised by the FDA in connection with designating albuterol non-essential. Our research represents our independent views on the current and projected market environments for selling albuterol. NERA specializes in applying microeconomics to complex business and legal matters. For over 40 years, NERA economists have contributed to understanding the economic issues in business, legal, regulatory, and public policy forums.

03P-0029 RPT 1

Please contact me if you have any comments or questions.

Sincerely,

Richard R. Rozek

RPR:pmb
Enclosure
cc: John K. Jenkins, Director
Office of New Drugs, Food and Drug Administration

Robert J. Meyer, Director
Office of Drug Evaluation II, Food and Drug Administration

Eugene J. Sullivan, Medical Officer
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Dr. Stuart Nightingale, M.D., Chief Medical Officer
Department of Health and Human Services

THE IMPACT ON PATIENTS AND PAYERS OF DESIGNATING ALBUTEROL A NON-ESSENTIAL USE OF AN OZONE DEPLETING SUBSTANCE

by

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Prepared in Response to Citizen Petition of the U.S. Stakeholders Group on MDI Transition (FDA Docket No. 03P-0029)

September 8, 2003

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THE IMPACT ON PATIENTS AND PAYERS OF DESIGNATING ALBUTEROL A NON-ESSENTIAL USE OF AN OZONE DEPLETING SUBSTANCE

by

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and
Emily R. Bishko
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Washington, DC*

I. INTRODUCTION AND SUMMARY

Over twenty years ago, the U.S. Food and Drug Administration ("FDA") approved albuterol dispensed in metered dose inhalers ("MDIs") propelled by chlorofluorocarbons ("CFCs"). The product is widely used to treat asthma and chronic obstructive pulmonary disease ("COPD").[1] In the intervening period, the U.S. government ratified the Montreal Protocol[2] and thereby agreed to phase out ozone depleting substances ("ODSs") such as CFCs. The Protocol Parties allowed for an essential use exemption that covers CFC MDIs, but only when no technically and economically feasible alternatives exist. Subsequently, the FDA

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* Senior Vice President and Analyst, respectively, at National Economic Research Associates, Inc. ("NERA"). NERA is a Marsh & McLennan company. MMC is a global professional services firm with annual revenues exceeding $10 billion. GlaxoSmithKline provided financial support for the economic research described in this paper.

[1] Albuterol MDI is a rapid-acting inhaled beta-2 agonist used to relieve acute asthma and COPD exacerbations and is often referred to as a quick relief or rescue medicine. National Institute of Health ("NIH"), "Global Initiative for Asthma, Global Strategy for Asthma Management and Prevention," Revised 2002, pp. 103 and 111 and FDA, Center for Drug Evaluation and Research, *Electronic Orange Book*, ("Electronic Orange Book"), http://www.fda.gov/cder/ob/default.htm. Albuterol MDIs are currently indicated for treating or preventing bronchospasm with reversible obstructive airway disease and for preventing exercise-induced bronchospasm. Ventolin® HFA Inhalation Aerosol (GlaxoSmithKline) and Proventil® HFA Inhalation Aerosol (Schering), *Physicians Desk Reference Electronic Library*, 57th Ed. Montvale, NJ, 2003.

[2] "The Montreal Protocol on Substances that Deplete the Ozone Layer," United Nations Environment Programme ("UNEP"), http://www.unep.ch/ozone/montreal.shtml, ("Montreal Protocol"). The legal framework in the U.S. associated with the Montreal Protocol is the Clean Air Act.

approved two albuterol non-CFC MDIs[3] and these products are now available to patients with asthma or COPD.

In July 2002, the FDA published a final rule to establish "the standard it will use to determine which FDA-regulated products that utilize an ODS are essential under the Clean Air Act."[4] As the FDA has previously recognized, removing the essential use designation for albuterol means those products delivered via CFC MDIs will no longer be available to patients.[5] The U.S. Stakeholders Group on MDI Transition submitted a Citizen Petition to the FDA in January 2003 requesting that the agency initiate a rulemaking to remove albuterol CFC MDIs from the list of essential uses of ODSs.[6] In considering whether to designate albuterol in CFC MDIs non-essential, one of the criteria identified by the FDA is whether patients will be adequately served after this change in policy.[7]

We prepared an economic analysis to determine the impact on patients and payers when the FDA designates albuterol CFC MDIs non-essential. We compared the costs for albuterol MDIs to patients and payers under two scenarios:

- the current state of the world and

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[3] Non-CFC albuterol MDIs use hydrofluoroalkane ("HFA") as the propellant.

[4] Department of Health and Human Services, FDA, 21 CFR Part 2, Docket No. 97N-0023, RIN 0910-AA99, "Use of Ozone-Depleting Substances; Essential-Use Determinations," *Federal Register*, Vol. 67, No. 142, July 24, 2002 ("FDA Final Rule"), p. 48370.

[5] Department of Health and Human Services, FDA, 21 CFR Part 2, Docket No. 97N-0023, RIN 0910-AA99, "Use of Ozone-Depleting Substances; Essential-Use Determinations," *Federal Register*, Vol. 64, No. 169, September 1, 1999, p. 47736.

[6] "Citizen Petition Submitted by the U.S. Stakeholders Group on MDI Transition ("Citizen Petition")," January 29, 2003, and Citizen Petition Supplement, July 21, 2003. The U.S. Stakeholders Group consists of the following organizations representing patients and medical professionals: the Allergy and Asthma Network/Mothers of Asthmatics; American Academy of Allergy, Asthma and Immunology; American Academy of Pediatrics; American Association for Respiratory Care; American College of Allergy, Asthma and Immunology; American College of Chest Physicians; American Lung Association; American Thoracic Society; and Asthma and Allergy Foundation of America. Also see "Comments Regarding Citizen Petition Submitted by U.S. Stakeholders Group on MDI Transition Docket #03P-0029," prepared by E.J. Allera, June 3, 2003; and "Comments on Citizen Petition on Removing Albuterol MDI from FDA's List of Essential ODS Uses (FDA Docket 03P-0029) Submitted by GlaxoSmithKline," July 2, 2003 ("GSK Comments").

[7] FDA Final Rule, p. 48374. Also see "Montreal Protocol on Substances that Deplete the Ozone Layer," *UNEP Report of the Technology and Economic Assessment Panel*, May 2003 ("TEAP Report"), pp. 103 and 110.

- the projected state of the world when the FDA designates albuterol MDIs non-essential.

In our projected scenario, we assumed conservatively that payers will receive no additional rebates or discounts beyond the levels specified for brand albuterol HFA MDI products under the Omnibus Budget Reconciliation Act of 1990 ("OBRA 90"). However, rebates paid by manufacturers to government and private payers for albuterol HFA MDI products may actually be larger due to the competitive market environment.

The vertical structure of the marketplace for selling pharmaceutical products such as albuterol is complex. It includes the following participants:

- manufacturers;
- wholesalers or distributors;
- retailers, non-federal hospitals, government agencies, HMOs, clinics, federal facilities;
- third-party payers (government and private); and
- patients.

In conducting our analysis, we analyzed the participants in the U.S. healthcare system described by this vertical structure to determine the impact on patients of designating albuterol CFC MDIs non-essential. Using data from IMS Health ("IMS"), Verispan, and other public sources, we determined the revenues and associated costs to the relevant participants in the U.S. healthcare system for each scenario. We then measured the impact of the FDA determining albuterol CFC MDIs are non-essential on patients and payers as the difference between the values derived from the two scenarios.

We estimated the average increase in total costs per MDI to be $9.87 where

- patients pay an average increase of $7.33 per MDI and
- third-party payers pay an average increase of $2.54 per MDI.

In addition, we calculated the average daily increase in costs in the U.S. healthcare system during the first year after the FDA designates albuterol CFC MDIs non-essential to be

- $0.005 [or .5¢] per capita or
- $0.044 [or 4.4¢] per asthma/COPD patient.

In subsequent years, the impact on the healthcare system is likely to be lower due to the competitive market environment.

Of course, the values we calculated are averages. As discussed below, many patients will experience no increase in costs. Patients with insurance pay higher co-payments for brand compared to generic products. It is this patient group that will bear a substantial portion of the increase in costs for albuterol MDIs. Most importantly, a patient who needs albuterol MDIs, but is unable to pay for the product, will not have to forego treatment. A large number of patients receive pharmaceutical products through various federal and state government programs. Manufacturer-sponsored discount and patient assistance programs such as *Bridges to Access*, *Orange Card*, and *Together Rx* are also available. The availability of two albuterol non-CFC MDIs together with these programs provide that patients will be adequately served when the FDA determines that albuterol in CFC MDIs is non-essential. Moreover, implementing this policy change is consistent with the overall U.S. commitment to the Montreal Protocol.

We explain our analysis in detail in the remainder of the paper, which is organized as follows:

- Background (Section II),
- Measuring the Costs to Patients and Payers (Section III),
- Financial Results (Section IV),
- Mitigating Factors (Section V), and
- Conclusion (Section VI).

II. BACKGROUND

A. History of Competition

In May 1981, the FDA approved two CFC MDI products

- Proventil® — submitted by Schering-Plough Corporation ("Schering") and
- Ventolin® — submitted by GlaxoSmithKline ("GSK").[8]

These products were the only versions of albuterol in MDIs available from May 1981 to December 1995. During this period, Schering and GSK competed for sales and access to formularies (lists of preferred pharmaceutical products) used for patients covered by selected government and private insurance programs. To understand the extent of price competition, we compared the monthly weighted average retail acquisition prices for Proventil® and Ventolin® from January 1992 and December 1995.[9] The prices range from $9.87 to $17.84 per MDI. In addition to dispersion of prices for a given product, we also observed fluctuations in relative prices. See Exhibit 1 for the comparison of the average prices of the two products from July 1993 through June 1994.

In December 1995, patents for albuterol CFC MDIs expired, and the first generic manufacturer, IVAX, Inc. ("IVAX"), received FDA approval.[10] Subsequently, the FDA approved three additional Abbreviated New Drug Applications for generic versions of albuterol in CFC MDIs.[11]

B. Montreal Protocol and the Clean Air Act

Since the 1970s, the U.S. government has become increasingly aware that a number of chemicals including CFCs break down the ozone layer.[12] For example, the U.S. government

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[8] Information provided by the FDA, Center for Drug Evaluation and Research, July 11, 2003.

[9] Derived from IMS data. Data prior to 1992 are not available in electronic form.

[10] Electronic Orange Book.

[11] In addition to IVAX, the FDA approved Armstrong Pharmaceuticals, Genpharm, and Sidmark Laboratories to sell albuterol inhalers. Electronic Orange Book.

[12] "Ozone Science: The Facts Behind the Phaseout," U.S. Environmental Protection Agency ("EPA"), http://www.epa.gov/ozone/science/sc_fact.html ("EPA Ozone Science").

banned CFC propellants in aerosol cans in 1978.[13] Depleting ozone causes increased incidence of skin cancer, cataracts, and other illnesses.[14] The U.S. government accepted the Montreal Protocol and implemented the associated programs under Title VI of the Clean Air Act to end production and use of ODSs including CFCs.[15] Since January 1, 1996, CFCs have been phased out of most consumer products.[16] However, the FDA designated certain medical products such as albuterol CFC MDIs as essential until sufficient alternatives were available.[17]

In December 2000, the Protocol Parties issued Decision XII/2 entitled "Measures to facilitate the transition to chlorofluorocarbon-free metered-dose inhalers."[18] In response, 12 European countries determined that albuterol CFC MDIs are no longer essential: Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Luxembourg, Portugal, The Netherlands, Norway, and the U.K.[19] In addition, Canada, Australia, and Japan have eliminated the use of albuterol in CFC MDIs.[20] The U.S. remains an outlier among the major developed countries in eliminating albuterol CFC MDIs.

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[13] "The Plain English Guide to the Clean Air Act," EPA, http://www.epa.gov/oar/oaqps/peg_caa/pegcaa06.html ("EPA Summary").

[14] EPA Ozone Science.

[15] EPA Ozone Science.

[16] EPA Summary.

[17] FDA Final Rule, p. 48371.

[18] "Report of the Twelfth Meeting of the Parties," *UNEP*, http://www.unep.org/ozone/mop/12mop/12mop-9.e.shtml, January 10, 2001.

[19] Countries other than the U.S. refer to albuterol as salbutamol. "List of Non-Essential Substances," *UNEP*, http://www.unep.org/ozone/dec12-2-3.pdf and GSK Comments, p. 2.

[20] GSK Comments, p. 2.

C. Incentives for Pharmaceutical R&D

Both the Montreal Protocol and Clean Air Act created incentives for companies to invest resources in R&D into technologies to replace albuterol CFC MDIs.[21] The opportunity to develop such technologies was available to all companies, including existing brand and generic manufacturers of albuterol MDIs, since the patents for the underlying chemical compound had already expired.[22]

We understand that the FDA required pharmaceutical manufacturers to prepare a complete New Drug Application ("NDA") for any albuterol product using non-CFC MDIs. In general, the average R&D cost for a new chemical entity is $802 million[23] and takes up to 15 years to develop and receive FDA approval.[24] One of the current manufacturers of CFC-free albuterol, GSK, invested nearly $1 billion in R&D over the past three decades in non-CFC delivery systems, including approximately $500 million for dry powder inhalers ("DPIs") and $400 million for MDIs.[25] As of January 1999, Boehringer Ingelheim had invested approximately $272 million in "the development of HFA-propellant based MDIs and new propellant-free devices."[26] 3M reported on the scope of its R&D efforts that "[f]inding an acceptable alternative to CFCs required not only a change in propellant, but also corresponding

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[21] Markets for other consumer products responded similarly. In some cases, the impending phase-out of CFCs provided an impetus to invest in R&D into new or alternative technologies that resulted in net savings and/or improved products. For example, the Aerospace Guidance and Metrology Center tested alternatives to CFC-based cleaning solvents for missile guidance systems and won the Ford Foundation "Innovations in American Government" in 1995 for the novel cleaning processes. The center moved from consuming "more than 2 million pounds per year of CFC-based cleaning solvents" to virtually no reliance on CFCs. "Benefits of CFC Phase-out," EPA, http://www.epa.gov/ozone/geninfo/benefits.html.

[22] Electronic Orange Book.

[23] Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics*, Vol. 22, 2003, pp. 151-185. More recently, the estimate of the cost of drug development has been raised to $1.4 billion per new molecular entity. "R&D Execs Paint Bleak Picture of Industry Productivity: $1.4 Bil. Per NME," *The Pink Sheet*, August 18, 2003, p. 6.

[24] Bertram Spilker, "The Drug Development and Approval Process," *New Medicines in Development for Infectious Diseases*, Pharmaceutical Research and Manufacturers of America, July 25, 2003.

[25] These estimates include the capital expenditures by GSK to date for both types of devices.

[26] Equal to DM 500 million divided by the average monthly exchange rate in 2001 of 1.8359 DM/US$. "Boehringer Ingelheim at the Forefront of Non-CFC Respiratory Device Development," Boehringer Ingelheim News, http://www.boehringer-ingelheim.com/corporate/asp/news/nprint.asp?ID=37, January 19, 1999, and Federal Reserve Bank of St. Louis, Germany/U.S. Foreign Exchange Rate, http://research.stlouisfed.org/fred2/series/exgeus/downloaddata, last updated December 1, 2001.

changes to the entire MDI system, including manufacturing methods, components and formulation."[27] Other pharmaceutical companies have also invested resources to developing non-CFC respiratory products including AstraZeneca, Aventis, IVAX, and Schering.[28] These investments have already yielded a variety of new technologies such as breath-actuated delivery devices, dose counters, enhanced DPIs, and mini-nebulizers.[29] In the future, the resulting new, improved products will increase treatment options available to patients and stimulate greater price competition among sellers.

As a result of the R&D activities, pharmaceutical companies successfully developed alternatives to albuterol CFC MDIs. The HFA propellant was identified as a viable alternative to CFC in albuterol MDIs. The FDA approved

- Proventil® HFA in 1996 — submitted by Schering and
- Ventolin® HFA in 2001 — submitted by GSK.[30]

Other firms are in the process of seeking FDA approval for albuterol products with non-CFC delivery devices. For example, IVAX submitted two NDAs to the FDA for a proprietary albuterol HFA MDI and a CFC-free albuterol in its patented breath-actuated Easi-Breathe® inhaler on February 3 and September 2, 2003, respectively.[31] Sepracor, Inc. ("Sepracor") is conducting Phase III clinical trails for levalbuterol HFA MDI and in early 2002 entered into a manufacturing collaboration with 3M Drug Delivery Systems Division for its HFA MDI.[32]

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[27] "Inhalation Drug Delivery: Get the Edge in a Competitive Environment," 3M Drug Delivery Systems, http://www.3m.com/us/healthcare/manufacturers/dds/pdf/idd_brochure.pdf, p. 6.

[28] TEAP Report, pp. 111-112.

[29] "Your Metered-Dose Inhaler Will Be Changing—Here Are the Facts," NIH, National Heart, Lung, and Blood Institute, http://www.nhlbi.nih.gov/health/public/lung/asthma/mdi.htm.

[30] Electronic Orange Book.

[31] "IVAX Submits New Drug Application for CFC-Free Albuterol," and "IVAX Submits First NDA for Easi-Breathe in U.S.," February 3, and September 2, 2003, respectively. IVAX press releases available at http://www.ivax.com.

[32] Levalbuterol is a purified form of albuterol that is currently available as a nebulizer solution. "Science & Medicine, Respiratory," Sepracor, http://www.sepracor.com/science/index.cfm?s= 1A#. "Right Better than Left in Asthma Medication for Children," National Jewish Medical and Research Center, December 31, 2001, http://www.njc.org/news/levalbuterol_2001.html.

Additional entry is likely since 3M has expressed an interest in forming other partnerships to apply the 3M delivery technologies such as HFA.[33]

Pharmaceutical companies responded to the R&D incentives created by the Montreal Protocol by introducing new products. However, patients, physicians, pharmacists, and payers have been and will continue to be slow at adopting these new products unless the FDA determines that albuterol CFC MDIs are non-essential.

III. MEASURING THE COSTS TO PATIENTS AND PAYERS

A. FDA Criteria — Patients Adequately Served

The FDA identified several criteria that it will consider when deciding whether to remove CFC MDIs from the list of essential ODSs. With respect to albuterol, the FDA has approved two safe and effective albuterol HFA MDIs used to treat asthma and COPD. The albuterol HFA MDIs have the same indication and convenience of use as the CFC MDIs, and are available in sufficient quantities and have adequate post-marketing data. However, the "FDA will also consider whether a high-priced non-ODS product is effectively unavailable to a portion of the patient population because they cannot afford to buy the product."[34] To address this remaining criteria over whether patients will be adequately served after the FDA designates albuterol CFC MDIs non-essential, we measured the change in costs to patients, the government, and private third-party payers.

B. Description of Data

1. Overview

For our study, we relied initially on IMS data.[35] IMS is a commercial data service that provides market research, business analysis, forecasting, and sales analyses to the

[33] "3M Seeking Partners for its Biotech Drug Delivery Technologies," 3M press release, June 10, 2002, http://www.3m.com/us/healthcare/manufacturers/dds/jhtml/press_releases.jhtml.

[34] FDA Final Rule, p. 48374.

[35] We supplemented IMS data with other sources such as Verispan, the National Association of Chain Drug Stores, and the American Lung Association. Similarly, we relied on governmental sources such as the Census Bureau.

pharmaceutical industry worldwide. Specifically, we utilized IMS Retail Perspective®/Provider Perspective® data that contain national sales estimates of pharmaceutical products purchased by retail drugstores, mail order pharmacies, and non-retail type outlets from wholesalers. These data include revenues and unit sales of albuterol by product (e.g., MDIs), manufacturer, and channel.[36]

2. Total Annual Volume

IMS collects data using a sampling methodology and does not include all channels for distribution of pharmaceutical products. As a result, IMS often under-reports the total sales of products. To adjust for IMS under-reporting the use of albuterol, we reviewed the total annual unit sales from 1992 through 2002.[37] Demand for albuterol MDIs is relatively constant over time regardless of changes in price and number of sellers. After adjusting the IMS sample data, we estimated total annual market demand for albuterol MDIs of 50,000,000 units. We concluded that annual volume has been relatively stable and is likely to remain stable when the FDA designates albuterol CFC MDIs non-essential. See Exhibit 2.[38]

There are approximately 20,300,000 people in the U.S. diagnosed with asthma and 10,515,000 with COPD.[39] Allocating the 50,000,000 units of albuterol sold annually across the two patient groups yields an average of 1.6 units per asthma or COPD patient. Patients do not always use pharmaceutical products according to the recommended dosing requirements. For example, adhering to the treatment regimens for asthma is a continuing issue. One study[40] found factors that affect compliance with asthma treatments are side effects of medication, cost, time constraints, poor understanding of the disease, lack of physician interest in treating the

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[36] The 13 channels currently used by IMS are: chain stores, clinics, federal facilities, food stores, HMO, home healthcare, independent, long-term care, miscellaneous (other), prisons, universities, mail order, and non-federal hospitals.

[37] IMS began measuring prescription sales through mail order as a separate channel in 1998. We adjusted IMS data for each year from 1992 through 1997 for mail order prescription sales by adding the average units sold in 1998 and 1999 of 5,009,000 units.

[38] Other events occurred with regard to treating asthma and COPD between 1992 and 2002. We identified selected marketplace events in Exhibit 2 as well.

[39] Data on patients with asthma or COPD based on the National Health Interview Survey, 2000 and 2001.

[40] Bruce G. Bender, "Overcoming Barriers to Nonadherence in Asthma Treatment," *Journal of Allergy and Clinical Immunology*, Vol. 109, June 2002, pp. S554-S559.

disease, and low patient interest in changing behavior or seeking treatment. Of these factors, motivating the patient is the most critical factor in improving compliance with asthma treatments.

C. Framework for Analysis

1. Market Scenarios

We undertook a comprehensive study of the flow of albuterol MDIs and associated annual revenues and costs through the entire U.S. healthcare system under two scenarios:

- the marketplace as it currently exists with annual volume of 50,000,000 units, brand and generic versions of albuterol CFC MDIs, and two brand versions of albuterol HFA MDIs; and
- the projected marketplace under the assumption that the FDA determines albuterol is non-essential and, thus, albuterol CFC MDIs are no longer available, while the two versions of albuterol HFA MDIs remain available and are sold at current brand HFA MDI prices.

We based our measures of prices and shares on the corresponding weighted average data from 2001 and 2002 for each IMS channel.

2. Vertical Structure of the Pharmaceutical Sector

The pharmaceutical sector has a complex vertical structure from innovator (brand manufacturers) and imitators (generic manufacturers) to the patient including the following participants.

- Manufacturers are of two types. Some manufacturers conduct R&D, obtain regulatory approvals, and market brand products. Other manufacturers do not develop products, but, rather, wait until the patents or other forms of exclusivity for the brand products expire and then offer generic versions of the products. Both brand and generic manufacturers must comply with the FDA regulations.

- Wholesalers (local, regional, and national) obtain products from manufacturers and resell the products to drug stores, food stores, hospitals,[41] or government agencies.
- Retailers, hospitals, and government agencies provide pharmaceuticals directly to patients based on instructions (e.g., prescriptions) from physicians.
- Third-party payers (government and private) collect premiums from tax revenues, employers, or patients to pay for all or part of the patients' pharmaceutical bill.
- Patients use pharmaceutical products to treat their diseases. Patients either pay all the costs for a product, or a third-party pays a share of the costs.

See Exhibit 3. Given that a central FDA concern is whether patients will be adequately served, we focused our analysis on patients and the associated costs borne by both patients and third-party payers in obtaining albuterol MDIs from retailers or other healthcare centers (e.g., clinics, hospitals, or universities).

3. Methodology

a. Overview

Using data from IMS and other commercial and government data sources, we examined the two states of the world (current and projected). For each state, we calculated how the costs for albuterol MDIs would be distributed across patients and third-party payers. We compared the annual current and projected scenarios to assess the impact of designating albuterol CFC MDIs as non-essential on costs borne by patients and third-party payers.

[41] In the hospital sector, Group Purchasing Organizations ("GPOs") negotiate prices for pharmaceutical products on behalf of member hospitals. A given hospital may be a member of several GPOs.

b. Grouping IMS Channels

We consolidated the 13 channels from the IMS data into four groups based on the magnitude of the average prices that IMS reported the members of the group paid during 2001 and 2002 and whether the channels paying relatively low prices were public or private institutions. We relied on IMS data to measure prices for this analysis. However, IMS data do not capture all the discounts or rebates available from manufacturers. We provide descriptive statistics on each of the groups in Exhibit 4.

Group 1 includes the IMS channels chain drug stores, independent drug stores, mail order pharmacies, food stores, long-term care facilities, home healthcare, and miscellaneous-other. Collectively, Group 1 represents 83.9 percent of reported units sold in IMS data. The payers for pharmaceutical products sold through the Group 1 channels (with share of total units) are of three types:

- Cash Payers (13.3 percent),
- Medicaid Payers (14.9 percent), and
- Insurance Payers (71.8 percent).

Information on shares of units is based on the shares of total retail sales (units) of albuterol MDIs in 2001 and 2002 to Cash, Medicaid, and Insurance Payers as reported by Verispan.[42]

Groups 2, 3, and 4, represent 4.3 percent, 6.0 percent, and 5.8 percent of units sold, respectively. The channels included in Groups 2, 3, and 4, are clinics, HMOs, and universities; non-federal hospitals; and federal facilities and prisons, respectively. For each group, we analyzed the costs borne by patients and third-party payers before and after the change in policy by the FDA regarding albuterol MDIs.

[42] Verispan is a commercial data service that provides a range of market research and data in the U.S. pharmaceutical industry.

c. Analysis[43]

To calculate the change in costs incurred by patients and third-party payers for albuterol MDIs due to the FDA action, it is important to understand the channels through which patients purchase albuterol MDIs and the extent to which third-party payers cover the costs. IMS reports sales from wholesalers to retailers, clinics, hospitals, or federal facilities. Therefore, we computed the acquisition costs for retailers, clinics, hospitals, and federal facilities and calculated the prices to patients and third-party payers. When applicable, we subtracted additional manufacturers' rebates paid directly to payers (e.g., Medicaid and Insurance Payers).

Patients obtaining albuterol MDIs through Group 1 channels purchase from retailers. To calculate the total brand and generic retail price per MDI, we applied the average retail mark-up to the weighted average retail acquisition cost (or wholesaler price) for brand and generic albuterol MDIs separately.

- Retailers' mark-ups on brand albuterol MDIs for Cash Payers, Medicaid Payers, and Insurance Payers are, on average, 28.8 percent, 28.8 percent, and 14.4 percent, respectively[44]
- Retailers' mark-ups on generic albuterol MDIs for Cash Payers, Medicaid Payers, and Insurance Payers are, on average, 363.3 percent, 234.5 percent, and 234.5 percent, respectively[45]

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[43] We provide references to summary exhibits throughout the text. For the details of the underlying calculations, see the Appendix available from the authors on request.

[44] Based on the weighted average price for brand albuterol MDIs to chain stores, food stores, and independent stores of $29.99 for the period May 2002 to February 2003, derived from IMS data, and the average retail price of $38.62 for the period May 2002 to April 2003 for the same channels, Verispan data. The retailer mark-up is equal to the average retail price of $38.62 less the average retail acquisition cost of $29.99, divided by the average retail acquisition cost or 28.8 percent. We assumed Insurance Payers negotiated a 50 percent discount on the retailer mark-up.

[45] Based on the weighted average price for generic albuterol MDIs to chain stores, food stores, and independent stores of $4.88 for the period May 2002 to February 2003, derived from IMS data, and the average retail price of $22.61 for the period May 2002 to April 2003 for the same channels, Verispan data. The retailer mark-up is equal to the average retail price of $22.61 less the average retail acquisition cost of $4.88, divided by the average retail acquisition cost or 363.3 percent. The retailer mark-up to Medicaid of 234.5 percent is based on a Federal Maximum Allowable Cost or MAC, which includes a dispensing fee of $19. We assumed Insurance Payers negotiate a discount similar to Medicaid. Individual states or insurers may implement lower prices than MAC.

We then subtracted additional manufacturer rebates paid directly to Medicaid and Insurance Payers. We assumed manufacturers' rebates to Medicaid Payers for brand and generic albuterol MDIs before the policy change are 30.0 percent and 11.0 percent of manufacturers' prices,[46] respectively, based on the guidelines in the OBRA 90.[47] We also assumed manufacturers' rebates to Insurance Payers for brand albuterol MDIs of 15.1 percent of manufacturers' prices based on our understanding of a minimum manufacturer rebate for a brand product. The total costs are equal to the retailers' prices less the manufacturers' rebates.

Next, we determined how the costs are divided among patients and third-party payers. In general,

- patients bear the full costs for cash purchases;
- the government bears all costs for patients with Medicaid coverage; and
- patients with insurance coverage pay differential co-payments for brand and generic drugs of $22 and $10, respectively, and the Insurance Payers bear the remaining costs.[48]

Patients unable to pay the cash price for their prescription drugs are eligible to participate in various patient assistance or discount programs. Some of the cash paying patients are covered by Medicare, which does not have a prescription drug benefit. However, such a benefit is currently being considered in Congress.[49]

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[46] Manufacturers' prices are equal to 96 percent of wholesalers' prices. The National Association of Chain Drugs Stores reported that for the average retail prescription cost, the manufacturer and wholesaler received 75.6 percent and 3.3 percent of the cost, respectively. IMS data reported sales at the wholesaler level. Thus, the total IMS wholesaler revenue represents 78.9 percent (75.6 percent+3.3 percent) of the total cost. The revenue due the manufacturer is 96 percent of the total amount reported by IMS (75.6 percent/78.9 percent). "Industry Statistics, Industry Facts-at-a-Glance, Pharmaceutical Pricing," National Association of Chain Drug Stores, http://www.nacds.org/wmspage.cfm?parm1=507.

[47] "Prescription Drugs, Expanding Access to Federal Prices Could Cause Other Changes," U.S. General Accounting Office, GAO/HEHS-00-118, August 2000. Also see William von Oehsen, "Pharmaceutical Discounts under Federal Law: State Program Opportunities," speech at the National Conference of State Legislatures Fifth Health Policy Conference, November 16, 2001.

[48] Based on data for the average co-payment in 2003 from "Strategic Health Plans Update 2002," *Health Strategies Group.*

[49] David Stout, "President Urges Compromise on Medicare Prescription Plan," *nytimes.com*, July 30, 2003, http://www.nytimes.com/2003/07/30/politics/30CND-MEDI.html.

We performed similar analyses for Groups 2, 3, and 4. For these groups,

- patients purchasing albuterol at clinics, universities, or through HMOs pay identical co-payments for brand and generic pharmaceutical products, and the associated organization bears the remaining costs;[50]
- non-federal hospitals bear all costs for patients obtaining albuterol through this channel; and
- the federal government bears all costs for patients obtaining albuterol through federal facilities.

The FDA designating albuterol CFC MDIs non-essential affects the costs incurred by patients if they are cash payers or have co-payments through their insurance coverage. It affects the costs to private third-party payers if they are Insurance Payers, clinics/HMOs/universities, or non-federal hospitals. Finally, it affects the costs to the government for sales to Medicaid payers or to federal facilities. For each group, we determined the total costs to patients and third-party payers (government and private) before the policy change by multiplying the brand and generic costs per MDI by the expected unit sales.

When the FDA designates albuterol CFC MDIs non-essential, only brand HFA MDIs will be available. We repeated the analyses described above assuming all MDIs will be sold at the current price for albuterol HFA. Accordingly, we assumed manufacturers' rebates to Medicaid decrease to the minimum 15.1 percent as mandated by OBRA 90 and Insurance Payers also receive rebates of 15.1 percent.[51] That is, we assumed conservatively that despite the lower prices and increased discounts currently available for brand and generic albuterol CFC MDIs, albuterol HFA MDIs will continue to be sold at its current prices with no additional discounts or rebates. As discussed below, competitive pressures will allow certain

[50] We assumed the co-payment is $5 for both brand and generic products.

[51] "Prescription Drugs, Expanding Access to Federal Prices Could Cause Other Changes," U.S. General Accounting Office, GAO/HEHS-00-118, August, 2000.

government and insurance payers to obtain discounts or rebates in excess of these levels. We estimated the total impact on patients and third-party payers of the FDA designating albuterol CFC MDIs non-essential as the projected costs less the current costs.

IV. FINANCIAL RESULTS

To determine the economic impact on patients and third-party payers due to the FDA designating albuterol CFC MDIs non-essential, we calculated the average change in costs per unit borne by patients and third-party payers (government or private). For each group, the change in total costs borne by patients and third-party payers divided by the associated projected annual unit sales yields the estimated change in cost per albuterol MDI.

- Cash-paying patients will pay an average increase of $8.61 per MDI, which may be mitigated by one or more factors as discussed below.
- Patients with Medicaid coverage or patients who acquire their MDIs at clinics/HMOs/universities, non-federal hospitals, or federal facilities/prisons will incur no increase in costs.
- Patients with private insurance obtaining albuterol MDIs through Group 1 channels will pay a higher price due to a differential co-payment for brand and generic products of $22 and $10, respectively. On average, they will pay an increase of $10.57 per MDI.[52]
- Overall, patients will incur an average cost increase of $7.33 per MDI.

Third-party payers (government and private) will be affected differentially by the FDA designating albuterol CFC MDIs non-essential.

- The cost per MDI for the private Insurance Payers in Group 1 will be reduced by $2.65. Insurance Payers will benefit since patients covered by their plans will pay higher average co-payments for brand pharmaceuticals, and some insurance

[52] The average difference in co-payments for brand and generic pharmaceutical products is $12. Since some patients are already using the brand albuterol, they are already paying the higher co-payment amount. The total cost increase we calculated reflects that these patients will experience no increase in their co-payment for brand albuterol MDIs.

payers will negotiate rebates from the competing manufacturers of albuterol in HFA MDIs, which they do not receive from the current generic manufacturers.

- The costs to other Payers (government and private Insurance Payers in Groups 2 and 3) will increase as a result of the policy change by $12.47 to $17.91 per MDI depending on the insurer and group with no more than the rebate percentage specified under OBRA 90.[53]
- Overall, third-party payers will incur an average cost increase of $2.54 per MDI.

See Exhibit 5.

The costs of changing regulatory policies are often expressed in terms of the costs per capita or costs per diagnosed patient. Using data on the current U.S. population and the number of patients diagnosed with asthma or COPD, we calculated the impact on these populations during the first year after the FDA action.

- The total daily increase in costs per capita will be $0.005 [or .5¢].
- The total daily increase in costs per asthma or COPD patient will be $0.044 [or 4.4¢].

See Exhibit 6. In subsequent years, competitive pressures in the marketplace will likely reduce these costs.

V. MITIGATING FACTORS

A. Programs to Help Specific Patients

Existing government and private sector programs help to protect certain patient groups from prices for prescription pharmaceutical products. In particular, they serve as an effective safety net against what otherwise might be the adverse impact of increased prices for albuterol MDIs when the FDA designates CFC MDIs non-essential.

[53] We applied the 15.1 percent rebate to insurance payers as well even though OBRA 90 does not mandate that these payers receive a rebate.

1. Government Programs

Potentially vulnerable patient populations such as the elderly, disabled, and poor should be able to obtain albuterol MDIs when the FDA removes albuterol CFC MDIs from essential use. Existing government programs such as Medicaid insulate many indigent patients from cost increases for pharmaceutical products. Other programs funded by state governments will further protect these vulnerable populations. "As of July 2, 2003 at least 38 states have established or authorized some type of program to provide pharmaceutical coverage or assistance, primarily to low-income elderly or persons with disabilities who do not qualify for Medicaid."[54] In addition, the elderly will likely have coverage for prescription pharmaceuticals through the federal Medicare program.

2. Private Sector Programs

a. Indigent Populations

GSK and Schering have developed a number of prescription drug programs that provide albuterol MDIs to patients who

- are not covered under government programs or
- do not have prescription drug coverage.

Programs to assist patients who are unable to afford prescription drugs include the following.

- *GW Patient Assistance Program* ("GW"),
- *SB Foundation Access to Care* ("SB"),
- *GSK Bridges to Access*, and
- *Schering Laboratories Patient Assistance Program.*

[54] "State Pharmaceutical Assistance Programs (includes seniors, disabled, uninsured and others)," National Conference of State Legislatures, updated July 15, 2003, http://www.ncsl.org/programs/health/drugaid.htm.

In June 2003, GSK replaced the GW and SB programs with *Bridges to Access*. These two legacy programs provided 289,000 patients nearly $100 million worth of medicines in 2001.[55]

GSK's new *Bridges to Access* program provides assistance to patients living in the U.S., regardless of citizenship. Similar to GSK's GW and SB programs, multi-person households with annual income at or below 250 percent of Federal Poverty Level or single-person households with annual income below $25,000 and whose costs of prescriptions are not covered by government programs or private medical insurance are eligible for the *Bridges to Access* program. It provides pharmaceuticals with a co-pay of $5 as well as case management services that help patients identify alternate funding sources for prescription drugs and other healthcare services. Ventolin® HFA is covered under the program. In 2002, GSK provided over $168 million worth of medicines to 400,000 patients through this program.[56]

Similarly, Schering developed the *Schering Laboratories Patient Assistance Program* to provide indigent patients access to prescription drugs including Proventil® MDIs. This program assists low-income patients who do not have private or public prescription drug insurance coverage and cannot afford treatment. Patients receive a three-month supply of a product as requested by the physician or patient. In 2002, Schering distributed pharmaceuticals free of charge to nearly 40,000 patients and dispensed over 66,000 prescriptions.[57] Thus, poor patients who do not have prescription coverage and are not covered under governmental programs will still have access to albuterol MDIs.

b. Elderly Populations

There are a number of manufacturer-sponsored programs designed to assist the elderly including the following.

[55] "Performance with Integrity," GSK, http://www.gsk.com/ser/2001/ser01/CSR.pdf.

[56] "Bridges to Access," GSK, http://bridgestoaccess.gsk.com/index.html.

[57] Schering has a separate patient assistance program for cancer and hepatitis pharmaceuticals. The two indigent care programs combined provided 55,000 patients with approximately $160 million worth of products. "Patient Assistance," Schering, http://www.sch-plough.com/patient.html.

- *Orange Card* and
- *Together Rx.*

GSK offers the *Orange Card* for seniors and the disabled enrolled in Medicare who have annual incomes below $30,000 (single) and $40,000 (couple) and are currently without public or private insurance coverage for prescription medicines. The *Orange Card* provides average savings of 30 percent per outpatient prescription. Ventolin® HFA MDIs are covered by the *Orange Card* program.[58]

Several pharmaceutical manufacturers including Abbott Laboratories, AstraZeneca, Aventis, Bristol-Myers Squibb Company, GSK, Johnson & Johnson, and Novartis sponsor the *Together Rx* prescription savings program. This program provides those Medicare enrollees with annual incomes below $28,000 (single) and $38,000 (couple) the opportunity to save 20-40 percent on over 170 prescription products including Ventolin®.[59]

In sum, government and private sector programs exist for vulnerable patient populations to provide access to low-cost or free albuterol MDIs after the FDA action. Information about these programs is readily available. Patients have been obtaining pharmaceutical products including albuterol through these programs.

B. Competitive Market Environment

The number of firms in a market does not necessarily need to be large to achieve competitive results.[60] Conversely, a large number of firms in a market does not necessarily guarantee a competitive outcome. Assessing the extent of competition must move beyond

[58] *Orange Card*, GSK, http://us.gsk.com/card/.

[59] "Savings and Medicines, Together," *Together Rx*, http://www.togetherrx.com/about.html.

[60] In the case of cellular telephones, effective competition in the cellular mobile telephone service exists with two market participants.

numbers alone to consider characteristics of the market.[61] For example, one should also focus on the relative size of the firms.

The Horizontal Merger Guidelines ("Guidelines"), issued by the U.S. Department of Justice and the U.S. Federal Trade Commission, use the Herfindahl-Hirschman Index ("HHI") as one indicia of market competition. "The HHI takes into account the relative size and distribution of the firms in a market and approaches zero when a market consists of a large number of firms of relatively equal size. The HHI increases both as the number of firms in the market decreases and as the disparity in size between those firms increases."[62] Lower values of the HHI are associated with a more competitive market. Assuming albuterol MDIs constitute a market, we calculated the HHI to be 5,070 based on the units of brand and generic albuterol MDIs sold by wholesalers in 2002.[63] While seven firms had unit sales reported by IMS greater than 0.5 percent of total unit sales, the market is concentrated due to the existence of a single dominant firm, Schering, that represented 69 percent of total units sales in 2002.[64]

We also calculated the HHI for the albuterol MDI market after the FDA determines albuterol is non-essential. GSK and Schering will compete to sell Ventolin® HFA and Proventil® HFA. Prior to generic entry in December 1995, GSK and Schering were the only two firms to sell brand albuterol CFC MDIs. We calculated each firm's expected market share for brand albuterol HFA MDIs based on their average annual share of unit sales from 1992 through 1995.[65] Using these shares, we estimated that the HHI with two sellers is 5,050. The projected market concentration is slightly lower than the current level of 5,070. See Exhibit 7.

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[61] The performance of particular markets depends on the conduct of the buyers and sellers, which evolves from the structure of the market. The number of buyers and sellers is only one of the structural characteristics. See F.M. Scherer and David Ross, *Industrial Market Structure and Economic Performance*, Third Edition, Houghton Mifflin Company, Boston, 1990, pp. 4-5.

[62] Guidelines, Para. 1.51, http://www.usdoj.gov/atr/public/testimony/hhi.htm.

[63] Calculated by squaring the market share of each firm competing in the market, based on unit sales in 2002, and then summing the resulting numbers.

[64] Schering sells both brand and generic albuterol MDIs. Warrick Pharmaceuticals is the subsidiary of Schering that sells generic versions of albuterol. Some sellers of albuterol may merely be re-selling albuterol MDIs purchased from a manufacturer approved by the FDA. Analyses of competitiveness in the market typically consolidate all sales controlled by a given manufacturer.

[65] IMS recorded the first sales of generic albuterol CFC MDIs in January 1996.

When the FDA designates albuterol CFC MDIs as non-essential, the structure of the marketplace will change from one characterized by a single large seller and several smaller sellers to one with two sellers of approximately equal size. Fewer, equally sized firms in a market provide approximately the same level of market concentration as the situation where one seller is significantly larger in terms of unit sales than the other sellers.

C. Large Buyers

Another important characteristic of pharmaceutical markets is the presence of large organizations such as private insurers, federal government, GPOs, and pharmacy benefit managers ("PBMs"). These organizations represent large numbers of patients when negotiating prices for pharmaceutical products. As a result, they have bargaining power with manufacturers. For example, PBMs negotiate prices with manufacturers on behalf of their clients (e.g., insurers, employers, or government agencies). The four largest PBMs are Advance PCS, Medco Health Solutions, Express Scripts, Inc., and Caremark Rx, Inc. They provide benefits for 75 million, 65 million, 42 million, and 20 million people in the U.S., respectively.[66] These types of organizations stimulated competition between GSK and Schering in the past. They will also be able to exert buying or monopsony power to receive additional discounts on Ventolin® HFA and Proventil® HFA beyond those we assumed after the FDA designates albuterol CFC MDIs non-essential.

D. Savings in Healthcare Costs from Eliminating CFCs

While the change in FDA policy will cause a short-term increase in U.S. healthcare expenditures for albuterol MDIs, one should also consider the associated savings in healthcare expenditures due to the reduction in emission of CFCs. Scientists have documented that the ozone layer protects the environment from harmful ultraviolet rays and that eliminating CFCs, which deplete this protective ozone layer, will provide health benefits including reduced

[66] *Study of Pharmaceutical Benefit Management*, PriceWaterhouseCoopers LLP, HCFA Contract No. 500-97-0399/0097, June 2001, p. 7.

incidence of skin cancer (melanoma and non-melanoma), cataracts and other eye damage, human immune system suppression, and premature aging of the skin and other skin problems.[67]

1. Skin Cancer

Each year, approximately 1 million people in the U.S. are diagnosed with skin cancer.[68] A recent study quantified that a one-percent decrease in stratospheric ozone will result in about a two-percent increase in the incidence of non-melanoma skin cancer.[69] The average cost to treat non-melanoma is $492 per treatment session in physician offices, $1,043 in outpatient settings, and $5,537 in inpatient settings.[70] By eliminating CFCs, the "EPA expects 295 million fewer cases of non-melanoma skin cancer over the next century."[71]

2. Cataracts

Cataract surgery is the most common surgical procedure performed on Americans age 65 and older.[72] By age 80, more than half of all Americans develop cataracts.[73] The Environmental Management Authority reports a 0.6 percent to 0.8 percent increase in cataracts for every one-percent decrease in stratospheric ozone.[74] The average cost to treat cataracts is $1,644.[75] Thus, the increase in U.S. healthcare expenditures for albuterol MDIs will be offset by decreases in healthcare expenditures for other diseases including skin cancer and cataracts.

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[67] "Health Effects of Overexposure to the Sun," EPA, http://www.epa.gov/sunwise/uvandhealth.html.

[68] National Cancer Institute, http://www.nci.nih.gov/cancerinfo/wyntk/skin.

[69] More than 1.2 million Americans will develop non-melanoma skin cancer in 2000 while more than 1,900 will die from the disease. "Health Effects of Overexposure to the Sun," EPA, http://www.epa.gov/sunwise/uvandhealth.html. "Benefits of CFC Phaseout," EPA, http://www.epa.gov/ozone/geninfo/benefits.html.

[70] Doctors Guide, http://www.pslgroup.com/dg/1f4202.htm.

[71] "Benefits of CFC Phaseout," EPA, http://www.epa.gov/ozone/geninfo/benefits.html.

[72] "UV Radiation and the Eye," University of Colorado and NOAA's Air Resources Laboratory, http://www.srrb.noaa.gov/UV/resources/uveyes_final.pdf.

[73] National Eye Institute, http://www.nei.nih.gov/news/pressreleases/032002.htm.

[74] Environmental Management Authority, http://www.nalis.gov.tt/Agri/agri_weather_OzoneDepletionHumanHealth.html.

[75] Information provided by American Society of Cataract and Refractive Surgery, April 10, 2003.

VI. CONCLUSION

We analyzed the impact on patients and third-party payers of the FDA determining albuterol CFC MDIs are non-essential to determine if patients would be adequately served. Patients paying cash or co-payments will incur higher costs, while those patients relying on the government (e.g., Medicaid or federal facilities), clinics/HMOs/universities, or hospitals will experience no change in costs. The government (federal and state), clinics/HMOs/universities, and hospitals and will incur higher costs. On average, at current prices for albuterol HFA products, patients will pay an additional $7.33 per albuterol MDI and third-party payers will pay an additional $2.54 per albuterol MDI.

The additional U.S. healthcare expenditures for albuterol MDIs due to the FDA policy change are offset by several factors. Most importantly, pharmaceutical manufacturers responded to the incentives created by the Montreal Protocol regarding CFCs. They invested in R&D to create new, improved products to treat asthma and COPD. These manufacturers also have patient assistance programs to provide that patients have access to albuterol MDIs. These programs, together with Medicaid, other state-sponsored programs, and the proposed coverage of prescription pharmaceutical products under Medicare, make it more likely that patients will not be denied access to albuterol MDIs due to lack of ability to pay. In sum, patients will continue to be adequately served when the FDA designates albuterol CFC MDIs non-essential pharmaceutical products.